REMARKS

Applicant has considered the non-final office action mailed November 26, 2008 in connection with the above-identified patent application.

Claims 1 – 6, 9-11, 15, 19-24, 27, 28, and 32 are pending in the instant Application. As of the instant reply, claims 4, 6, 9, 10, 15, 21 – 24, 27 and 32 are withdrawn from consideration.

Amendments to the Claims

Applicant amends claim 1, herein to delete references to solvates and prodrugs, and to insert instead of the latter "an in vivo hydrolysable ester or an in vivo hydrolysable amide".

Deletion of options from a list of alternatives raises no new matter issues. Hydrolysable esters and amides find support in the application specification (see WO2004/006899, the publication of the international application of which the instant application is the U.S. national phase) at, *e.g.*, page 40, lines 29 – 31.

Accordingly, no new matter is introduced by way of the new claims herein and entry thereof is respectfully requested.

REJECTIONS OF THE CLAIMS

Rejections under 35 U.S.C. § 112 (¶ 1)

The Examiner has rejected claims 1 – 3, 5, 11, 19 – 20, and 28 under 35 U.S.C. § 112 (first paragraph) as allegedly being based on a non-enabling disclosure.

In particular, the Examiner alleges that the specification enables neither solvates of IBAT inhibitors nor solvates of pharmaceutically acceptable salts of IBAT inhibitors, citing in particular to Grant *et al.*, *Adv. Drug Deliv. Rev.* (2001). Without conceding to the Examiner's position, Applicant amends herein claim 1 to delete the recitations of solvates and, accordingly, respectfully requests that the rejection be removed.

The Examiner has rejected claims 1 – 3, 5, 11, 19 – 20, and 28 under 35 U.S.C. § 112 (first paragraph) as allegedly failing to comply with the written description requirement. Applicant respectfully traverses the rejection.

Specifically, the Examiner objects to the recitation of "prodrugs" in claim 1. With the claim amendments herein, Applicant deletes "prodrug" from claim 1 and inserts in its stead, "an in vivo hydrolysable ester or an in vivo hydrolysable amide". This category of compound is

described in Applicant's specification at least at page 40, line 29 – page 41, line 21, including, examples of such compounds.

Accordingly, Applicant submits that claim 1, as amended herein, complies with the written description requirement of 35 U.S.C. § 112 (1st paragraph) and respectfully requests that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1 – 3, 5, 11, 19 – 20, and 28, under 35 U.S.C. § 103(a) as allegedly being obvious over WO 02/32428, ("Starke et al. '428"), in view of WO 02/50051 ("Starke et al. '051") and U.S. Patent No. 5,811,388 ("Friend, et al.").

The framework under which obviousness of a patent claim is judged was set forth by the U.S. Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), and is as follows. Under § 103:

- the scope and content of the prior art are to be determined;
- differences between the prior art and the claims at issue are to be ascertained; and
- the level of ordinary skill in the pertinent art resolved.

Based upon the answers to these factual enquiries, the obviousness or nonobviousness of the claimed subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might also be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Accordingly, and at a minimum, in order to establish obviousness of a claim, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Furthermore, and in instances where each and every limitation of the claimed invention can be found in a combination of references, an analysis of an apparent reason to combine the known elements in the fashion claimed should be made explicit. *KSR Int'l. Co. v. Teleflex Inc.*, (550 U.S. ___, 127 S. Ct. 1727 (2007)).

Additionally, dependent claims are nonobvious under 35 U.S.C. § 103 "if the independent claims from which they depend are nonobvious." In re Fine 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03.

To summarize the basis of the Examiner's rejection (set forth on pages 9 – 13 of the November 26, 2009 office action), it is that: Starke *et al.* '428 teach that 1,5-benzodiazepines with a sulphone and an amine in the 7-member ring are a class of IBAT inhibitors; a specific such IBAT inhibitor falling within the class recited in Starke *et al.*, and corresponding to one recited in Applicant's claims, is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; Friend *et al* teaches to utilize calcium phosphate in a pharmaceutical formulation for, *e.g.*, aiding in the delayed release and regional delivery profile. Applicant respectfully traverses, on at least the following grounds.

First, Applicant's disclosure describes experiments that show calcium salts to be effective in lowering bile salt concentrations in aqueous solutions. Hence Applicant shows that a combination therapy such as that claimed is useful in preventing or mitigating the diarrhea that would result from an excess of bile acids in the intestine following administration of an effective amount of an IBAT inhibitor. (Inhibiting ileal bile acid transport (IBAT), though desirable for other reasons, leads to a concomitant increase in bile acids that are not recycled in the intestine, thereby leading to irritation, including diarrhea. WO 2004/006899 at pages 1 – 2). Experimental data (*in vivo* and *in vitro*) described at pages 41 – 47 of Applicant's specification establishes that calcium induced bile acid binding arises from both bile acids adsorbing calcium phosphate particles, and unconjugated bile acids forming insoluble calcium salts.

With respect to the cited references, although both Starke '428 and Starke '051 describe classes of, and specific examples of, IBAT inhibitors, which themselves may be mixed with excipients, there is no teaching or disclosure to select particular excipients or to choose metal salts for any particular reason. In fact, for example, Starke '428 at page 8 describes various controlled-release formulations of IBAT inhibitors (without referencing metal salts), and at page 7 describes possible use of a "bile acid binder with colon release" as a way to offset diarrhea. However, this latter teaching involves use of a resin (Starke '428 at page 7, line 25), not a metal salt.

Friend *et al.*, on the other hand, despite referencing use of "non-gas forming mineral salts suchas alkaline earth (*e.g.*, Ca^{+2}, Mg^{+2}) phosphates" (Col. 12, lines 3 – 4), do not reference IBAT inhibitors amongst the classes of pharmaceuticals for which such excipients would be

appropriate, and do not at all give one of ordinary skill in the art any guidance as to selection of an appropriate excipient in Applicant's circumstances. Thus, the list of excipients disclosed in Friend *et al.*, is vast, and includes such diverse chemical forms as "cellulosic derivatives", "polyoxyethylene polymers", "colloidal silica", "natural hydrocolloid material", the aforementioned mineral salts, and "polyvinylpyrrolidone". There is nothing in Friend *et al.* that provides guidance to one deploying IBAT inhibitors which, *if any*, of such excipients would be appropriate for altering the salvation profile of bile acids liberated when using an IBAT inhibitor.

Accordingly, Applicant respectfully submits that the claims are non-obvious over the cited combination of references and requests that the rejection be removed.

Non-statutory (obviousness-type) Double Patenting Rejections

Due to the large number of such rejections, and due to the fact that arguments presented in support of double-patenting largely track those advanced to support a finding of obviousness and have been rebutted hereinabove, in connection with the rejections over Starke '428, Starke '051, and Friend *et al.*, Applicant hereby abbreviates and consolidates remarks responsive to the various grounds of rejection based on double-patenting considerations.

In short, and in each case of alleged double patenting, the Examiner states that, although the conflicting claims (the various pending claims of the instant application, and specific claims of the patent in question) are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope, when taking into consideration the teachings of Friend *et al.*

Specifically, on the ground of non-statutory obviousness-type double patenting, the Examiner has rejected:

1. claims 1 – 3, 5, and 11 as being unpatentable over claims 1 – 18 of U.S. Patent No. **7,192,945**, in view of Friend et al.;
2. claims 19 – 20 and 28 as being unpatentable over claims 1 – 18 of U.S. Patent No. **7,192,945** in view of Friend et al. and Starke et al. (WO 02/32428);
3. claims 1 – 3, 5, and 11 as being unpatentable over claims 1 – 10 of U.S. Patent No. **6,906,058** in view of Friend et al.;

4. Claims 19 – 20 and 28 as being unpatentable over claims 1 – 10 of U.S. Patent No. **6,906,058** in view of Friend et al. and Starke et al.[1];
5. Claims 1 – 3, 5, and 11 as being unpatentable over claims 1 – 6 and 8 of U.S. Patent No. **7,192,947** in view of Friend et al.;
6. Claims 19 – 20 and 28 as being unpatentable over claims 1 – 6 and 8 of U.S. Patent No. **7,192,947** in view of Friend et al. and Starke et al.[2];
7. Claims 1 – 3, 5, and 11 as being unpatentable over claims 1 – 11 and 13 of U.S. Patent No. **7,192,946** in view of Friend et al.;
8. Claims 19 – 20 and 28 as being unpatentable over claims 1 – 11 and 13 of U.S. Patent No. **7,192,946** in view of Friend et al. and Starke et al.[3];
9. Claims 1 – 3, 5, and 11 as being unpatentable over claims 1 – 11 and 13 of U.S. Patent No. **7,132,416** in view of Friend et al.;
10. Claims 19 – 20 and 28 as unpatentable over over claims 1 – 11 and 13 of U.S. Patent No. **7,132,416** in view of Friend et al. and Starke et al.[4];
11. Claims 1 – 3 and 11 as being unpatentable over claims 1 – 10 and 12 of U.S. Patent No. **7,238,684** in view of Friend et al.;
12. Claims 19 – 20 and 28 as being unpatentable over claims 1 – 10 and 12 of U.S. Patent No. **7,238,684** in view of Friend et al. and Starke *et al.*[5];
13. Claims 1 – 3, 11, 19 – 20 and 28 as being unpatentable over claims 1 – 9 and 13 – 15 of U.S. Patent No. **7,226,943** in view of Friend et al.; and
14. claims 1 – 3 and 11 as being unpatentable over claims 1 – 9 and 11 of U.S. Patent No. **7,125,864** in view of Friend et al.

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[1] According to the Examiner, this is a "provisional" rejection (Office Action, at page 18), though Applicant understands this *not* to be the case.

[2] According to the Examiner, this is a "provisional" rejection (Office Action, at page 20), though Applicant understands this *not* to be the case.

[3] According to the Examiner, this is a "provisional" rejection (Office Action, at page 22), though Applicant understands this *not* to be the case.

[4] According to the Examiner, this is a "provisional" rejection (Office Action, at page 24), though Applicant understands this *not* to be the case.

[5] According to the Examiner, this is a "provisional" rejection (Office Action, at page 26), though Applicant understands this *not* to be the case.

In essence, as argued hereinabove in connection with the rejections under 35 U.S.C. § 103(a), the various patent references that are cited as a basis for double-patenting rejections recite compounds or classes of compounds that have IBAT inhibitory activity. Those same patent references do not in themselves call for addition of metal ion salts, for example, as excipients, to improve release profiles or to mitigate symptoms of diarrhea in patients receiving IBAT inhibitors.

Friend *et al.*, teaches a large number of diverse excipients, including alkaline earth metal ion salts, but does not provide any indication that any will be appropriate for use with an IBAT inhibitor and provides one of ordinary skill in the art with no guidance or preference as to which to choose for such an application.

Accordingly, withdrawal of the various double-patenting rejections is respectfully requested.

By responding in the foregoing remarks only to particular positions taken by the examiner, Applicant does not acquiesce with other positions that have not been explicitly addressed. In addition, Applicant's selecting particular arguments for the patentability of a claim should not be understood as implying that no other reasons for the patentability of that claim exist. Finally, the applicant's decision to amend or cancel any claim should not be understood as implying that the applicant agrees with any positions taken by the examiner with respect to that claim or other claims affected by such amendments.

CONCLUSION

In view of the above remarks, Applicant respectfully submits that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 839-5070.

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No fee is believed owed in connection with filing of this amendment and reply, other than the extension of time fee, separately authorized herewith. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (ref. no. 23854-0006US1) for the appropriate amount.

Respectfully submitted,

Date: May 26, 2009 By: /Richard G. A. Bone/ 56,637
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